

PCTWORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁵ : A61K 31/11, 31/15, 31/155 A61K 31/205, 31/185, 31/19 A61K 31/195, 31/165	A2	(11) International Publication Number: WO 93/03714 (43) International Publication Date: 4 March 1993 (04.03.93)
(21) International Application Number: PCT/US92/06536 (22) International Filing Date: 11 August 1992 (11.08.92) (30) Priority data: 750,059 27 August 1991 (27.08.91) US 750,569 27 August 1991 (27.08.91) US (60) Parent Applications or Grants (63) Related by Continuation US 750,569 (CIP) Filed on 27 August 1991 (27.08.91) US 750,059 (CIP) Filed on 27 August 1991 (27.08.91) (71) Applicant (for all designated States except US): THE UPJOHN COMPANY [US/US]; 301 Henrietta Street, Kalamazoo, MI 49001 (US).	(72) Inventors ; and (75) Inventors/Applicants (for US only) : COLCA, Jerry, R. [US/US]; 8181 Contingo, Kalamazoo, MI 49009 (US). LARSEN, Scott, D. [US/US]; 2212 Sycamore Lane, Kalamazoo, MI 49008 (US). MEGGLASSON, Martin, Durham [US/US]; 5337 Whippoorwill, Kalamazoo, MI 49002 (US). TANIS, Steven, P. [US/US]; 7601 Farmington Avenue, Kalamazoo, MI 49002 (US). (74) Agent: CORNELGIO, Donald, L.; Corporate Intellectual Property Law, The Upjohn Company, 301 Henrietta Street, Kalamazoo, MI 49001 (US). (81) Designated States: AU, BB, BG, BR, CA, CS, FI, HU, JP, KP, KR, LK, MG, MN, MW, NO, PL, RO, RU, SD, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, SN, TD, TG). Published <i>Without international search report and to be republished upon receipt of that report.</i>	
(54) Title: A METHOD FOR TREATMENT OF METABOLIC DISORDERS AND METABOLISM (57) Abstract A method for treating or preventing non-insulin (Type II) diabetes mellitus by administering to an animal, including humans, a compound selected from Table 1 or a pharmaceutically acceptable salt thereof; and a method for treating or preventing excess adiposity or obesity by administering to an animal, including humans, a compound selected from Table 2 or a pharmaceutically acceptable salt thereof.		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	FI	Finland	MN	Mongolia
AU	Australia	FR	France	MR	Mauritania
BB	Barbados	GA	Gabon	MW	Malawi
BE	Belgium	GB	United Kingdom	NL	Netherlands
BF	Burkina Faso	GN	Guinea	NO	Norway
BG	Bulgaria	GR	Greece	NZ	New Zealand
BJ	Benin	HU	Hungary	PL	Poland
BR	Brazil	IE	Ireland	PT	Portugal
CA	Canada	IT	Italy	RO	Romania
CF	Central African Republic	JP	Japan	RU	Russian Federation
CG	Congo	KP	Democratic People's Republic of Korea	SD	Sudan
CH	Switzerland	KR	Republic of Korea	SE	Sweden
CI	Côte d'Ivoire	LI	Liechtenstein	SK	Slovak Republic
CM	Cameroon	LK	Sri Lanka	SN	Senegal
CS	Czechoslovakia	LU	Luxembourg	SU	Soviet Union
CZ	Czech Republic	MC	Monaco	TD	Chad
DE	Germany	MG	Madagascar	TC	Togo
DK	Denmark	ML	Mali	UA	Ukraine
ES	Spain			US	United States of America

A METHOD FOR TREATMENT OF METABOLIC DISORDERS AND METABOLISM

FIELD OF INVENTION

5 The present invention provides a new use for known compounds. More particularly, the present invention provides a method of treating or preventing certain metabolic disorders of human and animal metabolism, such as non-insulin dependent diabetes mellitus (NIDDM) by the administration of the compounds listed in Table 1, below and excess adiposity or obesity by the administration of the compounds listed in Table 2, below.

10 Other indications which may be treated by the subject method can include hyperglycemia, impaired glucose tolerance, hyperinsulinemia, insulin insensitivity, hyperamylinemia or hyperlipidemia.

BACKGROUND OF THE INVENTION

There are several metabolic disorders of human and animal metabolism, e.g., hyperglycemia, 15 impaired glucose tolerance, hyperinsulinemia and insulin insensitivity, hyperamylinemia, excess adiposity, and hyperlipidemia. Some or all of the above disorders may occur in the following disease states: non-insulin dependent diabetes mellitus (NIDDM), obesity, hypertension and atherosclerosis.

Hyperglycemia is a condition where the blood glucose level is above the normal level in 20 the fasting state, following ingestion of a meal, or during a provocative diagnostic procedure, e.g., a glucose tolerance test. It can occur in NIDDM as well as obesity. Hyperglycemia can occur without a diagnosis of NIDDM. This condition is called impaired glucose tolerance or pre-diabetes. Impaired glucose tolerance occurs when the rate of metabolic clearance of glucose from the blood is less than that commonly occurring in the general population after a standard dose of glucose has 25 been orally or parenterally administered. It can occur in NIDDM as well as obesity, pre-diabetes and gestational diabetes.

Hyperinsulinemia is defined as having a blood insulin level that is above normal level in the fasting state, following ingestion of a meal or during a provocative diagnostic procedure. It can be seen in NIDDM or obesity and can be associated with or causal in hypertension or 30 atherosclerosis. Hyperinsulinemia can occur without a diagnosis of diabetes. It may occur prior to the onset of NIDDM. Insulin insensitivity, also called insulin resistance, occurs when the insulin-dependent glucose clearance rate is less than that commonly occurring in the general population during diagnostic procedures such as a hyperinsulinemic clamp (See, e.g., DeFronzo, R. A. et al., Am. J. Physiol. 232:E214-E233, (1979)) or a minimal model test. See, e.g., Bergman, R. N. et al., 35 J. Clin. Invest. 68:1456-1467 (1981). Insulin insensitivity is considered also to occur when the blood glucose concentration is higher than that commonly occurring in the general population after

SUBSTITUTE SHEET

intravenous administration of insulin (insulin tolerance test) or when the ratio of serum insulin-to-glucose concentration is higher than that commonly occurring in the general population after a 10-16 hour fast. Insulin insensitivity may be found in NIDDM or obesity and can also be associated with or causal to hypertension or atherosclerosis.

5 Hyperamylinemia is defined as having an abnormally high blood amylin level. Amylin is also known as diabetes associated peptide (DAP) and insulinoma associated polypeptide (IAP). Hyperamylinemia can be seen in NIDDM or obesity.

Excess adiposity can be seen in NIDDM associated with obesity as well as obesity without NIDDM. It is defined as a higher fat body mass-to-lean body mass ratio than that commonly
10 occurring in the general population as measured by whole body specific gravity or other generally accepted means.

Hyperlipidemia is defined as having an abnormal level of lipids in the blood. Hyperlipidemia exists when the serum concentration of total cholesterol or total triglycerides or the serum concentration of LDL-cholesterol/HDL-cholesterol is higher than that commonly occurring
15 in the general population. It can be seen in NIDDM or atherosclerosis.

The above disease states could be treated by either ameliorating or preventing the metabolic and biochemical disorders. In addition, humans and animals, which have not been diagnosed as having one of the above disease states but evidencing some or all of the disorders described above, could be benefitted by preventing the development of a currently recognized disease state.
20 Therefore, a compound that is useful in the treatment of hyperglycemia, impaired glucose tolerance, hyperinsulinemia, insulin insensitivity, hyperamylinemia, excess adiposity or hyperlipidemia could also be used to treat or prevent NIDDM, obesity, hypertension or atherosclerosis.

The subject invention provides a method for preventing or treating NIDDM using Compounds 1-119, listed in Table 1, their free bases, or their pharmacologically acceptable esters
25 and salts. Compounds 1-119, their free bases, or their pharmacologically acceptable salts may be administered individually as the sole active ingredient in a composition or combined with other compounds selected from Table 1. Compounds 1-119 are known compounds and their sources are identified in Table 1.

The dose of Compounds 1-119 to be used is between 0.1 and 500 mg/kg body weight daily.
30 The preferred dose is 1-50 mg/kg/day. Compounds 1-119 may be administered orally, buccally, sublingually, parenterally, intranasally, intrarectally, or topically in any suitable pharmaceutical formulation. The oral route is preferred.

The subject invention also provides a method of preventing or treating the obesity using Compounds 1-128, listed in Table 2, their free bases, or their pharmacologically acceptable esters
35 and salts. Compounds 1-128, their free bases, or their pharmacologically acceptable salts may be administered individually as the sole active ingredient in a composition or combined to form a

SUBSTITUTE SHEET

composition.

The dose of Compounds 1-128 to be used is between 0.1 and 500 mg/kg body weight daily. The preferred dose is 1-50 mg/kg/day. Compounds 1-128 may be administered orally, buccally, sublingually, parenterally, intranasally, intrarectally, or topically in any suitable pharmaceutical
5 formulation. The oral route is preferred.

INFORMATION DISCLOSURE STATEMENT

Guanidine, monoguanidine and diguanidine compounds have been shown to produce hypoglycemia. See, e.g., Watanabe, C., J. Biol. Chem. 33:253-265 (1918); Bischoff, F. et al., Guanidine structure and hypoglycemia 81:325-349 (1929). However, these compounds were
10 observed to be toxic. In 1957, biguanide derivatives, e.g. phenformin and metformin, were used clinically as anti-diabetic agents. Some members of this class continue to be used today while others have been withdrawn from the market or banned in the United States and most Western countries. See, e.g., Schafer, G., Diabete Metabol. (Paris) 9:148-163 (1983).

Gamma-guanidinobutyramide also known as Tyformin, and the HCl salt of Tyformin,
15 known as Augmentin, were investigated as potential anti-diabetic agents from the mid-1960's until the mid-1970's. While Augmentin produced hypoglycemia, it was reported to produce hypertension in dogs [See, e.g., Malaisse, W. et al., Horm. Metab. Res. 1:258-265 (1969)] and respiratory and circulatory collapse in rats and rabbits. See, e.g., Buckle, A. et al., Horm. Metab. Res. 3:76-81 (1971). The free acid of the amide was said to lack hypoglycemic activity [See, e.g., Beeson, M.
20 et al., Horm. Metab. Res. 3:188-192 (1971)].

British patent 1,153,424 discloses the use of certain esters and amides of guanidino-aliphatic acids in the treatment of diabetes mellitus where hyperuremia is present. The patent does not disclose that these compounds have an effect on hyperglycemia or any other symptom or pathological state related to diabetes. In a Canadian patent, 891509, the use of esters and amides
25 of guanidinoaliphatic acids were disclosed for treating hyperuremia and hyperglycemia in diabetes mellitus. As noted above, the biologic activity of a guanidino alkanolic acid was known to be different and less favorable so as to be ineffective compared to its amide for treating hyperglycemia.

British patent, 1,195,199 discloses the use of guanidino alkanolic acids or their amides or
30 esters in an insulin-containing, parenterally-administered composition for the treatment of hyperglycemia occurring in diabetes. According to this patent, the combining of a guanidino alkanolic acid, amide or ester with insulin reduces the risk of hypoglycemia as compared to insulin alone. British patent 1,195,200 discloses the use of guanidino alkanolic acids in a composition containing a guanidino alkanolic acid amide or ester derivative for the treatment of hyperglycemia
35 occurring in diabetes. In a subsequent British patent, 1,552,179, the use of guanidino alkanolic acids, their salts, amides or esters in combination with a gluconeogenesis inhibitor for treating

SUBSTITUTE SHEET

hyperglycemic conditions was disclosed. Metformin was cited as an inhibitor of gluconeogenesis. Biological data indicated that HL 523, the preferred guanidino alkanolic acid derivative, was inactive as a single agent in six of seven experiments where blood glucose concentration was measured in alloxan diabetic mice and only weakly active in the seventh study. Most notably, British patents
5 1,195,199, 1,195,200 and 1,552,179 do not claim utility for guanidino alkanolic acids, as the sole active component, in compositions for treating hyperglycemic symptoms in diabetes. Among the guanidino alkanolic acids tested, several were inactive as a single agent. Thus, a variety of guanidino alkanolic acids lack significant anti-diabetic activity and combination of these compounds with an agent of known anti-diabetic activity, e.g., metformin, is necessary to show beneficial activity.

10 Aynsley-Green and Alberti injected rats intravenously with 3-GPA, arginine, guanidine, 4-guanidinobutyramide, and 4-guanidinobutyric acid. Arginine and 3-GPA stimulated insulin secretion transiently, but did not affect the blood glucose concentration while the other compounds stimulated insulin secretion but produced a rise in blood glucose concentration. See, e.g., Aynsley-Green, A. et al., *Horm. Metab. Res.* 6:115-120 (1974). Blachier, et al., observed that 10 mM 3-
15 GPA stimulated insulin secretion by isolated rat islets in vitro. See, e.g., Blachier, F. et al., *Endocrinology* 124:134-141 (1989). The insulin response induced by 3-GPA was 55% of that occurring when arginine was tested at the same concentration. In rats fed a diet supplemented with 10 mg/g 3-GPA for 30-60 days, the heart glycogen content was increased. See, e.g., Roberts, J. et al., *Am. J. Physiol.* 243:H911-H916 (1982). Similarly, skeletal muscle glycogen content was
20 increased in rats fed chow supplemented with 10mg/g of 3-GPA for 6-10 weeks. Mice fed a diet supplemented with 3-GPA at 20 mg/g and supplied with drinking water containing 5 mg/ml 3-GPA for 7-12 weeks had serum glucose concentrations that did not differ significantly from mice receiving unsupplemented chow and water. See, e.g., Moerland, T. et al., *Am. J. Physiol.* 257:C810-C816 (1989).

25 With respect to adiposity, it is known that in some, but not all cases [See, e.g., Shoubridge, E. et al., *Biochem. J.* 232:125-131 (1985)], supplementation of the diet with 10-20 mg/g 3-GPA results in decreased body weight. See, e.g., Moerland, supra and Mahanna, D. et al., *Exper. Neurol.* 68:114-121 (1980). This effect has been attributed to decreased skeletal muscle mass and has not been attributed to reduced adiposity or decreased lipid storage. See, e.g., Mahanna, supra and
30 Shields, R. et al., *Lab. Invest.* 33:151-158 (1975).

What is needed in the art is a sole therapy to treat or prevent the underlying metabolic disorders in these conditions.

SUMMARY OF THE INVENTION

In one aspect, the present invention provides a method of treating or preventing the
35 metabolic disorder of NIDDM by administering to an animal exhibiting diabetes, including humans, an effective amount of a compound of Table 1 or a pharmaceutically acceptable salt thereof. Other

indications for which these compounds may be useful can include hyperglycemia, impaired glucose tolerance, hyperinsulinemia, hyperamylinemia, excess adiposity and/or hyperlipidemia. The method comprises the systemic administration of Compounds 1-119, listed in Table 1, their free bases, or their pharmacologically acceptable esters and salts to animals, including humans, suffering from

5 NIDDM.

In another aspect, the present invention provides a method of treating or preventing a metabolic disorder such as excess adiposity or obesity in a patient susceptible to or experiencing said disorder comprising the systemic administration of Compounds 1-128, listed in Table 2, their free bases, or their pharmacologically acceptable esters and salts.

10 DETAILED DESCRIPTION OF THE INVENTION

Table 1, Compounds 1-119, their free bases, or their pharmacologically acceptable salts may be administered individually as the sole active ingredient in a composition for treating non-insulin dependent diabetes mellitus.

The Table 1 compounds 1-119 of this invention are either commercially available or

15 may be prepared by methods published in the chemical literature as indicated below in Table 1.

TABLE 1

	COMPOUND NAME	SOURCE
	1. DL-Aspartic acid	Aldrich Chemical Co.
20	2. Guanidine, benzyl-, sulfate	Patent Belg. 667875; <u>Chem Abstr.</u> 65:5398g
	3. Carbamic acid, (2-aminoethyl)dithio-	<u>Org. Synth. Coll.</u> , Vol. III, 394
	4. Benzimidazole, 2-benzyl-	Aldrich Chemical Co.
25	5. Guanidine, (benzyloxy)-, cyclohexanesulfanate (salt) or Cyclohexanesulfanic acid, salt with (benzyloxy)guanidine	Neth. Appl. 6502701; <u>Chem. Abstr.</u> 64:8087b
	6. Acetic acid, guanidino- or Glycocyamine	Aldrich Chemical Co.
	7. Guanidine, 1-<2-(1-methylindol-3-yl)ethyl>-, nitrate	Aldrich Chemical Co.
30	8. Pseudourea, 2-butyl-2-thio-, hydrobromide	Neth. Appl. 6502701; <u>Chem. Abstr.</u> 64:8087e
	9. Guanidine, (2-phenoxyethoxy)-	A. Musashi, <u>Hoppe-Seylers Z. Physiol. Chem.</u> 297, 71 (1954)
	10. Crotonic acid, 4-amino-, trans-	Sigma Chemical Co.
TABLE 1 (Cont'd)		

	11. 3-Aminopropane sulfonic acid sodium salt	Sigma Chemical Co.
	12. Guanidine, <2-(octahydro-1(2H)-azocinyl)ethyl>-, sulfate(2:1) or Guanethidine sulfate or Ismelin	Aldrich Chemical Co.
5	13. Taurine	Aldrich Chemical Co.
	14. Guanidine, (3-phenylpropoxy)-	Neth. Appl. 6502701; <u>Chem. Abstr.</u> 64:8087b
	15. Guanidine, 1-(3,3-diphenylpropoxy)-, nitrate	Neth. Appl. 6502701; <u>Chem. Abstr.</u> 64:8087b
	16. Butyric acid, 4-amino-3-hydroxy-, (+-)-	Aldrich Chemical Co.
10	17. Nicotinic acid, 6-amino-	Aldrich Chemical Co.
	18. Acrylic acid, 3-amidino-, trans-	Patent NL 6612037; <u>Chem. Abstr.</u> 67:72463j
	19. Pseudourea, 2-benzyl-2-thio-, hydrochloride	Aldrich Chemical Co.
15	20. Acrylic acid, 3-amidino-, cis- or Antibiotic 220t\$2	Patent NL 6612037; <u>Chem. Abstr.</u> 67:72463j
	21. Guanidine, 1-(4-oxo-2-thiazolidinyl)-	Pfalz and Bauer, Inc.
	22. Guanidine, 1-(benyloxy)- 3,3-dimethyl-, cyclohexane-sulfamate	Neth. Appl. 6502701; <u>Chem. Abstr.</u> 64:8087f
20	23. Guanidine, 1-(benzyloxy)-2,3-diisopropyl-, hydrochloride	Neth. Appl. 6502701; <u>Chem. Abstr.</u> 64:8087g
	24. Guanidine, phenethyl-, hydrogen sulfate, ethanol solvate	Aldrich Chemical Co.
	25. 4-Imidazoleacetic acid, hydrochloride	Aldrich Chemical Co.
25	26. Guanidine, (4-aminobutyl)-, sulfate or Agmatine sulfate	Aldrich Chemical Co.
	27. 1-Piperidinecarboxamidine, sulfate	Aldrich Chemical Co.
	29. 5-Indancarboxaldehyde, amidinohydrazone	Aldrich Chemical Co.
	30. Guanidine, dodecyl-	Aldrich Chemical Co.
	31. Glyoxylic acid, phenylhydrazone	M. Petrarulo et al., <u>J. Chromatogr.</u> 465, 87 (1989)
30	32. Guanidine, (4-methyl-2-quinazolinyl)-, hydrochloride	Aldrich Chemical Co.
	33. N-(Aminoiminomethyl)morpholine	Pfalz and Bauer, Inc.
	34. Guanidine, (2-benzoxazolyl)-	Aldrich Chemical Co.
TABLE 1 (Cont'd)		

SUBSTITUTE SHEET

	35. Glycine, N-methyl-2-phenyl-, monohydrochloride	K.H. Pfoermer et al., <u>Helv. Chim. Acta</u> 63, 653 (1980)
	36. 2-Pyridinamine, N-<2-(4-chlorophenyl)ethyl>-	Aldrich Chemical Co.
5	37. Hydrazinium, 2-(2-carboxyethyl)-1,1,1-trimethyl hydroxide, inner salt, dihydrate	Y. Goldberg et al., <u>Dokl. Akad. Nauk SSSR</u> 294, 1387 (1987); <u>Chem. Abstr.</u> 108:167024w
	38. 1-Propanesulfonic acid, 3-<(aminoiminomethyl)thio>-	Aldrich Chemical Co.
	39. N-Acetimidoyl-beta-alanine	T. Wang, <u>J. Org. Chem.</u> 39, 3591 (1974)
10	40. α -Amino- β -guanidinopropionic acid	Sigma Chemical Co.
	41. 4-Guanidinobenzoic acid	Sigma Chemical Co.
	42. 2-trifluoromethylphenylguanidine carbonate	Parish Chemical Co.
	43. Phenylguanidine carbonate	Parish Chemical Co.
15	44. N-(Dithiocarbamoyl)guanidine	Aldrich Chemical Co.
	45. 2-Nitrophenylguanidine	Parish Chemical Co.
	46. 2-chlorophenylguanidine carbonate	Parish Chemical Co.
	47. 2,4-dichlorophenylguanidine carbonate	Parish Chemical Co.
	48. 2-methoxyphenylguanidine carbonate	Parish Chemical Co.
20	49. 2-methylphenylguanidine carbonate	Parish Chemical Co.
	50. 4-ethylphenylguanidine carbonate	Parish Chemical Co.
	51. p-phenyldiguanidine hexaacetate	Parish Chemical Co.
	52. 4-Chlorophenylguanidine	Parish Chemical Co.
	53. 3-methylphenylguanidine carbonate	K & K Rare and Fine Chemicals (ICN Biomedicals, Inc.)
25	54. N,N-Dimethylguanidine	Aldrich Chemical Co.
	55. 2-methylpropylguanidine	Aldrich Chemical Co.
	56. N-isopropylguanidine	Aldrich Chemical Co.
	57. 3-Guanidinobutyric acid	V.M. Rodionov et al., <u>Zhur. Obschchei Khim.</u> 18, 2023 (1948)
	58. 3-((Aminoiminomethyl)thio)propionic acid	Aldrich Chemical Co.
30	59. 3-(2-Pyridyl)aminopropionic acid	G.R. Lappin, <u>J. Org. Chem.</u> 23, 1358 (1958)
	60. 2-(4-chlorophenyl)ethylguanidine	Patent application DE 3312-516-A
TABLE 1 (Cont'd)		
	61. 1-Naphthylguanidine Nitrate	Aldrich Chemical Co.

SUBSTITUTE SHEET

	62. 2-(4-Methylphenyl)ethylguanidine	Patent application DE 3312-516-A
	63. 2-(4-Methoxyphenyl)ethylguanidine	Patent application DE 3312-516-A
	64. 2-(4-hydroxyphenyl)ethylguanidine	Sigma Chemical Co.
	65. Histidine hydrochloride	ICN Biochemicals
5	66. 3-((Methylaminoiminomethyl)thio)propionic acid, hydrochloride	W. Hanefeld, <u>Arch. Pharm. (Winheim. Ger.)</u> 310 , 273 (1977)
	67. β -Guanidinopropionic acid, ethyl ester hydrochloride	M. Schuster et al., <u>Biomed. Biochim. Acta</u> 49 , 519 (1990)
	68. 1-(4-Chlorophenyl)imidazole	Fairfield Chemical Co.
10	69. 3-(3-Pyridylamino)propionic acid	R.U. Baltrusis et al., <u>Lietuvos TSR Mokslu Akad. Darbai Ser. B</u> 117 (1962); <u>Chem. Abstr.</u> 58:3387e
	70. 3-(Phenylamino)propionic acid	F. Gavina et al., <u>Tetrahedron</u> 42 , 5641 (1986)
	71. Imidazole, 2-benzyl-, hydrochloride	Y. Amemiya et al., <u>Synth. Comm.</u> 20 , 2483 (1990)
	72. Pseudourea, 2-isopropyl-2-thio-, hydrobromide	Patent FR 1456265; <u>Chem. Abstr.</u> 67:109606m
15	73. Guanidine, 1-(2-indol-3-ylethyl)-, sulfate	J.L. LaMattina et al., <u>J. Med. Chem.</u> 33 , 543 (1990)
	74. Pseudourea, 2-diphenylmethyl-2-thio-, hydrobromide	Patent FR 2528038 A2; <u>Chem. Abstr.</u> 100:209383e
	75. 3H-2,3-Benzoxazine-3-carboxamidine, 1,4-dihydro-, hydrochloride	Patent US 3625967; <u>Chem. Abstr.</u> 76:59679a
20	76. 1-Piperazinecarboxamidine, 4-phenyl-, sulfate	Z. Zhou et al., <u>Hejishu</u> 31 (1985); <u>Chem. Abstr.</u> 106:4977d
	77. Cinnamaldehyde, amidinohydrazone, nitrate or Guanidine, 1-amino-, hydrazone with cinnamaldehyde, nitrate	Patent US 3383409; <u>Chem. Abstr.</u> 69:76893p
25	78. Guanidine, (benzylideneamino)-	G. Soman et al., <u>Biochem.</u> 25 , 4113 (1986)
	79. Pyridine, 2-((2-imidazolin-2-ylamino)methyl)-, hydriodide	M. Dubey et al., <u>Pharmazie</u> 33 , 268 (1978)
	80. 2-Imidazoline, 2-(2-thenylamino)-, hydriodide	J.W. McFarland et al., <u>J. Med. Chem.</u> 12 , 1066 (1969)
30	81. 1,3-Benzimidazolinedicarboxylic acid, 2-imino-, dimethyl ester	Patent GB 1351883; <u>Chem. Abstr.</u> 81:105512u

TABLE 1 (Cont'd)		
	82. Guanidine <(.alpha. - methylbenzylidene)amino>-, hydrochloride	Y. Miyamoto <u>Nippon Novaku Gakkaishi</u> 11, 39 (1986); <u>Chem. Abstr.</u> 106:213883j
	83. p-Tolualdehyde, amidinohydrazone	A.F. Hegarty et al., <u>J. Chem. Soc. Perk. Trans. 2</u> 2047 (1973)
5	84. Benzaldehyde, O-ethyloxine	E. Buehler, <u>J. Org. Chem.</u> 32, 261 (1967)
	85. Guanidine, <(p-chlorobenzylidene)amino>-, sulfate(2:1)	S. Gopalan et al., <u>Biochem.</u> 25, 4113 (1986)
	86. Guanidine, (cyclohexylmethyl)-, sulfate(2:1)	M. Pawlowski et al., <u>Acta Pol. Pharm.</u> 45, 42 (1988); <u>Chem. Abstr.</u> 110:212468y
10	87. 2H-Pyrimido<1,2-c>quinazoline, 3,4,6,7-tetrahydro-6-imino-, hydrobromide, hydrate	R. Kwok, <u>J. Het. Chem.</u> 15, 877 (1987)
	88. Guanidine, N,N'-dimethyl-N''-(phenylmethyl)-, sulfate(2:1) or Bethanidine sulfate	Patent HU 155717; <u>Chem. Abstr.</u> 70:114811r
15	89. Guanidine, (4-hydroxybutyl)-, sulfate(2:1)	C. Yu. <u>Zhongcaoyao</u> 16, 6 (1985); <u>Chem. Abstr.</u> 102:226-092t
	90. Guanidine, propyl-, sulfate(2:1)	Patent WO 8400875; <u>Chem. Abstr.</u> 101:191387t
	91. 1H-Imidazol-2-amine, 4,5-dihydro-1-(phenylmethyl)-, monohydrochloride	F. Ishikawa et al., <u>Chem. Pharm. Bull.</u> 26, 3658 (1978)
20	92. 1H-Imidazol-2-amine, 4,5-dihydro-5-phenyl-1-(phenylmethyl)-, monohydrobromide	W.L. Matier et al., <u>J. Med. Chem.</u> 16, 901 (1973)
	93. Carbamimidothioic acid, <3-(trifluoromethyl)phenyl>methyl ester, monohydrochloride	L.A. Paquette et al., <u>J. Org. Chem.</u> 33, 1080 (1968)
25	94. Carbamimidothioic acid, (2,6-dichlorophenyl)methyl ester, monohydrochloride	J.J. Zalipsky et al., <u>J. Pharm. Sci.</u> 67, 256 (1978)
	95. 2-Isoindoline, 5-fluoro-2-(2-imidazolin-2-yl)	K. Kroeger et al., <u>Arzneim.-Forsch.</u> 40, 871 (1990)
	96. S-(2,4,6-trimethylbenzyl)isothioureia	C. Temple et al., <u>J. Org. Chem.</u> 41, 3784 (1976)
30	97. 4-Phenylbutylguanidine	B.R. Baker et al., <u>J. Med. Chem.</u> 12, 408 (1969)
	98. 3-Phenylpropylguanidine	E. Costa et al., <u>Life Sci.</u> 1, 75 (1962)
	99. 1,2,4-Triazolo<3,4-a>isoquinoline, 5,6-dihydro-3-(trifluoromethyl)-	Patent US 3823238; <u>Chem. Abstr.</u> 82:26146v
TABLE 1 (Cont'd)		

	100. 4(1H)-Pyrimidinone, 2,3-dihydro-2-imino-6-(3-nitrophenyl)	H.I. Skulnick et al., <u>J. Med. Chem.</u> 28, 1864 (1985)
	101. 2-Methyl-3-guanidinopropionic acid	E.L. Esmans, <u>Anal. Chem.</u> 56, 693 (1984)
5	102. Indole, 3-<(2-imidazolin-2-ylamino)methyl>-, hydriodide	
	103. 2-phenyl-2,2-dimethylethylguanidine	<u>J. Med. Chem.</u> 10:833 (1967)
	104. 2-phenyl-2-hydroxyethylguanidine	<u>J. Med. Chem.</u> 81:136057D
	105. 2,2-diphenylethylguanidine	<u>J. Med. Chem.</u> 10:833 (1967)
10	107. Guanidine, 1-<2-(1-indolyl)ethyl>-, nitrate	U.S. 3,093,632
	108. Guanidine, (3-indol-3-ylpropyl)-, nitrate	
	110. Guanidine, 1-(2-indol-1-ylethyl)-, nitrate	
	112. Guanidine, (5-methyl-2-benzimidazolyl)-	
15	115. Guanidine, <(2-chloro-6-fluorobenzylidene)amino>-, sulfate(2:1)	U.S. 3,975,533
	117. Methanimidamide, N'-(4-chlorophenyl)-N,N-dimethyl-	BE 627 317
	119. trans-2-Phenyl-1-quanidinocyclopropane	<u>J. Med. Chem.</u> 20:771 (1977)

SUBSTITUTE SHEET

The Table 2 compounds 1-128, their free bases, or their pharmacologically acceptable salts may be administered individually as the sole active ingredient in a composition.

The Table 2 compounds 1-128 of this invention are either commercially available or may be prepared by methods published in the chemical literature as indicated below in Table 2.

TABLE 2

	COMPOUND NAME	SOURCE
	1. DL-Aspartic acid	Aldrich Chemical Co.
	2. Guanidine, benzyl-, sulfate	Patent Belg. 667875; <u>Chem. Abstr.</u> 65:5398g
10	3. Carbamic acid, (2-aminoethyl)dithio-	<u>Org. Synth. Coll. Vol. III</u> , 394
	4. Benzimidazole, 2-benzyl-	Aldrich Chemical Co.
	5. Acetic acid, guanidino- or Glycocyamine	Aldrich Chemical Co.
15	6. Guanidine, (benzyloxy)-, cyclohexanesulfanate (salt), or Cyclohexanesulfanic acid, salt with (benzyloxy)guanidine	Neth. Appl. 6502701; <u>Chem. Abstr.</u> 64:8087b
	7. Guanidine, 1-(2-benzimidazolyl)- or Benzimidazole, 2-guanidino-	Aldrich Chemical Co.
	8. Pseudourea, 2-butyl-2-thio-, hydrobromide	Aldrich Chemical Co.
20	9. Guanidine, (2-phenoxyethoxy)-	Neth. Appl. 6502701; <u>Chem. Abstr.</u> 64:8087e
	10. Crotonic acid, 4-amino-, trans-	A. Musashi, <u>Hoppe-Seviers Z. Physiol. Chem.</u> 297, 71 (1954)
	11. 3-Aminopropane sulfonic acid sodium salt	Sigma Chemical Co.
	12. Butyric acid, 2,4-diamino-, L-, dihydrochloride	Sigma Chemical Co.
25	13. Guanidine, <2-(octahydro-1(2H)-azocinyl)ethyl>-, sulfate(2:1) or Guanethidine sulfate or Ismelin	Aldrich Chemical Co.
	14. Guanidine, (3-phenylpropoxy)-	Neth. Appl. 6502701; <u>Chem. Abstr.</u> 64:8087b
	15. Alanine, N-amidino-	A.E. Miller et al., <u>Synth.</u> 777 (1986)
30	16. Guanidine, 1-(3,3-diphenylpropoxy)-nitrate	Neth. Appl. 6502701; <u>Chem. Abstr.</u> 64:8087b
	17. Pyrazole-4-carboxylic acid, 3-amino-, ethyl ester	Aldrich Chemical Co.
	18. Nicotinic acid, 6-amino-	Aldrich Chemical Co.

TABLE 2 (Cont'd)	
	19. Acrylic acid, 3-amidino-, trans- Patent NL 6612037; <u>Chem. Abstr.</u> 67:72463j
	20. Pseudourea, 2-benzyl-2-thio-, hydrochloride Aldrich Chemical Co.
5	21. Acrylic acid, 3-amidino-, cis- or Antibiotic 220t\$2 Patent NL 6612037; <u>Chem. Abstr.</u> 67:72463j
	22. Guanidine, 1-(4-oxo-2-thiazolidinyl)- Pfalz and Bauer, Inc.
	23. Guanidine, 1-(benzyloxy)- 3,3-dimethyl-, cyclohexane-sulfamate Neth. Appl. 6502701; <u>Chem. Abstr.</u> 64:8087f
10	24. Guanidine, 1-(benzyloxy)-2,3-diisopropyl-, hydrochloride Neth. Appl. 6502701; <u>Chem. Abstr.</u> 64:8087g
	25. Guanidine, phenethyl-, hydrogen sulfate, ethanol solvate Aldrich Chemical Co.
	26. 4-Imidazoleacetic acid, hydrochloride Aldrich Chemical Co.
15	27. Guanidine, (4-aminobutyl)-, sulfate or Agmatine sulfate Aldrich Chemical Co.
	28. 1-Piperidinecarboxamidine, sulfate Aldrich Chemical Co.
	29. Guanidine, (5-methyl-2-benzimidazolyl)- Aldrich Chemical Co.
	30. 5-Indancarboxaldehyde, amidinohydrazone Aldrich Chemical Co.
20	31. Hydrocinnamic acid, .beta.-amino- Aldrich Chemical Co.
	32. Guanidine, dodecyl- Aldrich Chemical Co.
	33. Glyoxylic acid, phenylhydrazone M. Petrarulo et al., <u>J. Chromatogr.</u> 465, 87 (1989)
	34. Guanidine, (4-methyl-2-quinazolinyl)-, hydrochloride Aldrich Chemical Co.
25	36. Guanidine, (2-benzoxazolyl)- Aldrich Chemical Co.
	37. Hydrocinnamic acid, .beta.- (aminomethyl)-p-chloro- or Baclofen or Lioresal Sigma Chemical Co.
30	38. Glycine, N-methyl-2-phenyl-, monohydrochloride K.H. Pfoertner et al., <u>Helv. Chim. Acta</u> 63, 653 (1980)
	39. Hydrazinium, 2-(2-carboxyethyl)-1,1,1- trimethyl hydroxide, inner salt, dihydrate Y. Goldberg et al., <u>Dokl. Akad. Nauk SSSR</u> 294, 1387 (1987); <u>Chem. Abstr.</u> 108:167024w
	40. 1-Propanesulfonic acid, 3- <(aminoiminomethyl)thio>- Aldrich Chemical Co.

TABLE 2 (Cont'd)	
41. 1H-Pyrazole-1-propanic acid	H. Reimlinger et al., <u>Chem. Ber.</u> 97, 331 (1964)
42. N-Acetimidoyl-beta-alanine	T. Wang, <u>J. Org. Chem.</u> 39, 3591 (1974)
43. 2-Amino-3-guanidinopropionic acid	Sigma Chemical Co.
5 44. 2-Chloro-5-guanidinopentanoic acid	Sigma Chemical Co.
45. 4-Guanidinobenzoic acid, hydrochloride	Sigma Chemical Co.
46. 3-(Amino(phenylimino) methylamino)propionic acid	A.E. Miller et al., <u>Synth.</u> 777 (1986)
10 47. 2-trifluoromethylphenylguanidine carbonate	Parish Chemical Co.
48. Phenylguanidine carbonate	Parish Chemical Co.
49. N-(Dithiocarbamoyl)guanidine	Aldrich Chemical Co.
50. 2-Nitrophenylguanidine	Parish Chemical Co.
51. amidinothiourea	Alfa Research Chemicals
15 52. 2-chlorophenylguanidine carbonate	Parish Chemical Co.
53. 2,4-dichlorophenylguanidine carbonate	Parish Chemical Co.
54. 2-methoxyphenylguanidine carbonate	Parish Chemical Co.
55. 2-methylphenylguanidine carbonate	Parish Chemical Co.
56. 4-ethylphenylguanidine carbonate	Parish Chemical Co.
20 57. p-phenyldiguanidine hexaacetate	Parish Chemical Co.
58. 4-Chlorophenylguanidine	Parish Chemical Co.
59. 3-methylphenylguanidine carbonate	K & K Rare and Fine Chemicals (ICN Biomedicals, Inc.)
60. 1,1-Dimethylguanidine sulfate	Aldrich Chemical Co.
61. 2-Methylpropylguanidine sulfate	Aldrich Chemical Co.
25 62. 2-Guanidinopropane sulfate	Aldrich Chemical Co.
63. 3-Methyl-3-guanidinopropionic acid	V.M. Rodionov et al., <u>Zhur. Obschchei Khim.</u> 18, 2023 (1948)
64. 3-((Aminoiminomethyl)thio)propionic acid	Aldrich Chemical Co.
65. 2-Guanidinoethanesulfonic acid	J. Huxtable et al., <u>J. Pharmacol. Exp. Ther.</u> 211, 465 (1979)
66. 3-Phenyl-3-guanidinopropionic acid	V.M. Rodionov et al., <u>Zhur. Obschchei Khim.</u> 18, 2023 (1948); <u>Chem. Abstr.</u> 43:3793
30	TABLE 2 (Cont'd)

SUBSTITUTE SHEET

	67. 3-(2-Pyridylamino)propionic acid	G.R. Lappin, <u>J. Org. Chem.</u> 23, 1358 (1958)
	68. 3-Phenylpropylguanidine sulfate	E. Costa et al., <u>Life Sci.</u> 1, 75 (1962)
	69. 2-(4-Chlorophenyl)ethylguanidine sulfate	Patent application DE 3312-516-A
	70. 1-Naphthylguanidine nitrate	Aldrich Chemical Co.
5	71. 2-(4-Methylphenyl)ethylguanidine sulfate	Patent application DE 3312-516-A
	72. 2-(4-Methoxyphenyl)ethylguanidine sulfate	Patent application DE 3312-516-A
	73. 2-(4-Hydroxyphenyl)ethylguanidine sulfate	Sigma Chemical Co.
10	74. Histidine hydrochloride	ICN Biochemicals
	75. 3-((Methylaminoiminomethyl)thio)propionic acid, hydrochloride	W. Hanefeld, <u>Arch. Pharm. (Weinheim, Ger.)</u> 310, 273 (1977)
	76. 3-Guanidinopropionic acid, ethyl ester hydrochloride	M. Schuster et al., <u>Biomed. Biochim. Acta</u> 49, 519 (1990)
15	77. 2-Guanidinyloxyacetic acid	B.J. Ludwig et al., <u>J. Med. Chem.</u> 13, 60 (1970)
	79. 1-(4-Chlorophenyl)imidazole	F. Gavina et al., <u>Tetrahedron</u> 42, 5641 (1986)
	80. Imidazole, 2-benzyl-, hydrochloride	Y. Amemiya et al., <u>Synth. Comm.</u> 20, 2483 (1990)
	81. Pseudourea, 2-isopropyl-2-thio-, hydrobromide	Patent FR 1456265; <u>Chem. Abstr.</u> 67:109606m
20	82. Guanidine, 1-(2-indol-3-ylethyl)-, sulfate	J.L. LaMattina et al., <u>J. Med. Chem.</u> 33, 543 (1990)
	83. Pseudourea, 2-diphenylmethyl-2-thio-, hydrobromide	Patent FR 2528038 A2; <u>Chem. Abstr.</u> 100:209383e
	84. 3H-2,3-Benzoxazine-3-carboxamidine, 1,4-dihydro-, hydrochloride	Patent US 3625967; <u>Chem. Abstr.</u> 76:59679a
25	85. 1-Piperazinecarboxamidine, 4-phenyl-, sulfate	Z. Zhou et al., <u>Hejishu</u> 31 (1985); <u>Chem. Abstr.</u> 106:4977d
	86. Cinnamaldehyde, amidinohydrazone, nitrate or Guanidine, 1-amino-, hydrazone with cinnamaldehyde, nitrate	Patent US 3383409; <u>Chem. Abstr.</u> 69:76893p
30	87. Guanidine, (benzylideneamino)-	G. Soman et al., <u>Biochem.</u> 25, 4113 (1986)
	88. Pyridine, 2-<(2-imidazolin-2-ylamino)methyl>-, hydriodide	M. Dubey et al., <u>Pharmazie</u> 33, 268 (1978)
	89. 2-Imidazoline, 2-(2-thenylamino)-, hydriodide	J.W. McFarland et al., <u>J. Med. Chem.</u> 12, 1066 (1969)

TABLE 2 (Cont'd)		
	90. 1,3-Benzimidazolinedicarboxylic acid, 2-imino-, dimethyl ester	Patent GB 1351883; <u>Chem. Abstr.</u> 81:105512u
5	91. Guanidine, <(.alpha.-methylbenzylidene)amino>, hydrochloride	Y. Miyamoto <u>Nippon Novaku Gakkaishi</u> 11, 39 (1986); <u>Chem. Abstr.</u> 106:213883j
	92. p-Tolualdehyde, amidinohydrazone	A.F. Hegarty et al., <u>J. Chem. Soc. Perk. Trans. 2</u> 2047 (1973)
	93. Benzaldehyde, O-ethyloxime	E. Buehler, <u>J. Org. Chem.</u> 32, 261 (1967)
	94. Guanidine, <(p-chlorobenzylidene)amino>-, sulfate(2:1)	S. Gopalan et al., <u>Biochem.</u> 25, 4113 (1986)
10	95. Guanidine, (cyclohexylmethyl)-, sulfate(2:1)	N. Pawlowski, et al. <u>Acta Pol. Pharm.</u> 45, 42 (1988); <u>Chem. Abstr.</u> 110:212468y
	96. 2H-Pyrimido<1,2-o>quinazoline, 3,4,6,7-tetrahydro-6-imino-, hydrobromide. hydrate	R. Kwok, <u>J. Het. Chem.</u> 15, 877 (1978)
15	97. Guanidine, (2-hydroxyethyl)-, monohydrobromide	J.G. Sterk et al., <u>Arch. Pharm. (Weinheim. Ger.)</u> 319, 1057 (1986)
	98. Guanidine, N,N'-dimethyl-N''-(phenylmethyl)-, sulfate(2:1) or Bethanidine sulfate	Patent HU 155717; <u>Chem. Abstr.</u> 70:114811r
	99. Guanidine, propyl-, sulfate (2:1)	Patent WO 8400875; <u>Chem. Abstr.</u> 101:191387t
20	100. 1H-Imidazol-2-amine, 4,5-dihydro-1-(phenylmethyl)-, monohydrochloride	F. Ishikawa et al., <u>Chem. Pharm. Bull.</u> 26, 3658 (1978)
	101. 1H-Imidazol-2-amine, 4,5-dihydro-5-phenyl-1-(phenylmethyl)-, monohydrobromide	W.L. Matier et al., <u>J. Med. Chem.</u> 16, 901 (1973)
25	102. Carbamimidothioic acid, <3-(trifluoromethyl)phenyl>methyl ester, monohydrochloride	L.A. Paquette et al., <u>J. Org. Chem.</u> 33, 1080 (1968)
	103. Carbamimidothioic acid, (2,6-dichlorophenyl)methyl ester, monohydrochloride	J.J. Zalipsky et al., <u>J. Pharm. Sci.</u> 67, 256 (1978)
30	104. 2-Isoindoline, 5-fluoro-2-(2-imidazolin-2-yl)-, maleate	K. Kroeger et al., <u>Arzneim.-Forsch.</u> 40, 871 (1990)
	105. S-(2,4,6-trimethylbenzyl)isothiourea, hydrochloride	C. Temple et al., <u>J. Org. Chem.</u> 41, 3784 (1976)
	106. 4-Phenylbutylguanidine sulfate	B.R. Baker et al., <u>J. Med. Chem.</u> 12, 408 (1969)
35	107. .beta.-Alanine, N-(o-chlorophenyl)-	Patent FR 1514280; <u>Chem. Abstr.</u> 70:68195t

SUBSTITUTE SHEET

TABLE 2 (Cont'd)	
108. .beta.-Alanine, N-benzyl-, hydrochloride	P.W. Erhardt, <u>Synth. Comm.</u> 13, 103 (1983)
109. 1,2,4-Triazolo<3,4-a>isoquinoline, 5,6-dihydro-3-(trifluoromethyl)-	Patent US 3823238; <u>Chem. Abstr.</u> 82:26146v
5 110.	
111. 2-Phenyl-2-methylpropylguanidine sulfate	<u>J. Med. Chem.</u> 10:833 (1967)
112. Methanimidamide, N'-(4-chlorophenyl)-N,N-dimethyl-	BE 629 317
10 113. trans-2-Phenyl-1-guanidinocyclopropane sulfate	<u>J. Med. Chem.</u> , 20:771 (1977)
114. Butyric acid, 4-amino-3-hydroxy-, (.+.)-	
115. 2-Pyridinamine, N-<2-(4-chlorophenyl)ethyl>-	
15 116. 2-Methyl-3-guanidinopropionic acid	
117. 2-Phenyl-2-hydroxyethylguanidine sulfate	<u>J. Med. Chem.</u> 81:136-057D
118.	<u>J. Med. Chem.</u> 10:833 (1967)
20 120. Guanidine, 1-<2-(1-indolyl)ethyl>-, nitrate	US 3,093,632
123. Guanidine, 1-(2-indol-1-ylethyl)-, nitrate	US 3,028,393
128. Guanidine, <(2-chloro-6-fluorobenzylidene)amino>-, sulfate(2:1)	US 3,975,533

SUBSTITUTE SHEET

The subject compounds cause several biologic effects that are beneficial in the treatment of human disease. They improve plasma glucose level, insulin sensitivity, plasma amylin level, adiposity and plasma lipid level. All of these effects are beneficial in treating metabolic disorders or metabolism such as NIDDM and excess adiposity or obesity.

- 5 NIDDM is characterized by hyperglycemia in the fasting or post-prandial state and impaired glucose tolerance after oral or parenteral administration of a glucose solution. The subject compounds, that are administered to KKA^y mice, a rodent model of NIDDM, decreases the non-fasting plasma glucose concentration and improves glucose tolerance. The minimum effective dose in KKA^y mice is 130 mg/kg/d when administered as an admixture in rodent chow.
- 10 Higher doses produce a proportionately greater effect. Doses that are less than the minimum effective dose in KKA^y mice may be effective at decreasing blood glucose levels in other species, e.g., human, since elimination is rapid in rodents and may occur more slowly in other species.

- Impaired tissue insulin sensitivity and hyperinsulinemia occur in NIDDM [See, e.g.,
- 15 DeFronzo, R., Diabetes 37:667-687 (1988) and Reaven, G., Diabetes 37:1595-607 (1988)], hypertension (See, e.g., Reaven, supra), obesity (See, e.g., Glass A., supra), and atherosclerosis [See, e.g., Reaven, supra and Stout, R. W., Diabetologia 16:141-150 (1979)] and may be etiological factors in these diseases. 3-GPA ameliorates hyperinsulinemia in KKA^y mice and decreases the plasma ratio of insulin-to-glucose concentration, indicating increased insulin
- 20 sensitivity. Therefore, 3-GPA is useful in the treatment or in the prevention of NIDDM, hypertension, obesity, and atherosclerosis.

- Hyperamylinemia may occur in NIDDM, decreasing tissue glucose metabolism [See, e.g., Leighton, B. et al., Nature 335:632-635 (1988)] and altering pancreatic hormone secretion [See, e.g., Clark, A., Diabetic Medicine 6:561-567 (1989)]. 3-GPA ameliorates
- 25 hyperamylinemia and therefore is beneficial in treating disease states in which plasma amylin concentration is increased.

- Excess adiposity is an etiological factor in NIDDM and when extreme, represents a disease state in itself. The subject compounds decrease adiposity by decreasing the level of lipids stored in fat and liver tissue. The compounds are therefore beneficial in the treatment of
- 30 obesity alone or in concert with NIDDM. The effect of the subject compounds is selective for lipid-rich tissues (e.g., epididymal fat and fatty liver of ob/ob mice) while muscle mass is unaffected or only minimally affected.

- Increased serum low density lipoprotein (LDL) cholesterol concentration is an etiological factor in coronary artery disease. The subject compounds decrease LDL-cholesterol levels in
- 35 spontaneously hyperlipidemic mice and therefore is useful in treating or preventing hyperlipoproteinemia, atherosclerosis and coronary artery disease.

SUBSTITUTE SHEET

"Sole active pharmaceutical agent" means that the subject compounds or its salt, administered as claimed herein, is the only pharmaceutical agent in the composition.

"Patients susceptible to or experiencing a metabolic disorder," i.e., hyperglycemia, impaired glucose tolerance, hyperinsulinemia, insulin insensitivity, hyperamylinemia, excess adiposity and/or hyperlipidemia means a human or animal who exhibits said metabolic disorder and is therefore likely to exhibit one of more of the disease states described above. Such patients are readily diagnosed by a physician or veterinarian of ordinary skill. "Treatment" means the amelioration or total avoidance of the metabolic disorder as described herein. "Prevention" means the avoidance of a currently recognized disease state, as described herein, in a patient evidencing some or all of the metabolic disorders described above.

For all of these purposes, any convenient route of systemic administration is employed, e.g., orally, parenterally, intranasally or intrarectally. In general, the preferred form of administration is orally.

Compositions containing the compounds may be administered in a sustained release formulation. "Sustained release" means a formulation in which the drug becomes biologically available to the patient at a measured rate over a prolonged period. Such compositions are well-known in the art.

Since the subject compounds decrease body fat without affecting the lean mass, they are of great commercial benefit to the meat, poultry, and fish producing industries in achieving its goal of producing leaner animal products. The subject compounds can be administered admixed in the diet of farm animals or as a pharmaceutical preparation such as an oral tablet or capsule, by injection, or by implantable sustained release devices thereby increasing the protein content of the carcass while decreasing its fat content. This would produce muscle tissue with less fat. This benefit of the subject compounds would also impact on the potential health to the meat, poultry, and fish consuming public. The term "farm animals" is defined as animals which are raised for food production. The term includes, but is not limited to, such animals as cattle, poultry, fish, swine, and lamb.

The subject compounds increase exercise tolerance in normal mice. Thus the present invention may be useful in treating muscular dysfunction, such as post-poliomyelitis chronic muscle fatigue syndrome or muscular dystrophy, or in treating chronic muscular weakness associated with advanced age or chronic immobilization, or in increasing endurance and exercise in normal humans.

The subject compounds are also useful for improving the survival rate of mice maintained in a low oxygen environment and therefore is beneficial in treating or preventing disease states involving tissue hypoxia, e.g., peripheral claudication and exercise intolerance in diabetic humans, and angina, myocardial infarction and stroke in diabetic and normal humans.

SUBSTITUTE SHEET

It is known that glucose-dependent protein crosslinking alters the tertiary structure of several proteins. This protein glycosylation may contribute to diabetic complication and complications of aging in non-diabetic humans, such as neuropathy, nephropathy, retinopathy, hypertension, and atherosclerosis. The subject compounds are useful to block protein glycosylation and therefore be of benefit in treating or preventing this reaction.

The dosage regimen for the subject compounds in accord with this invention will depend on body weight. Table 1 and Table 2 compounds in pharmaceutical dosage form, can range from 1-500 mg/kg/day. The preferred dose is 5-100 mg/kg/day. Any sustained released formulations can be used.

The Table 1 compounds were tested for effects that are beneficial in the treatment or prevention of NIDDM using one or more of three procedures.

Procedure 1: Compounds were administered orally to KKA^y mice for 3 days. Compounds were mixed in the chow at 1-5 mg/g or unsupplemented chow was provided. The blood glucose concentration was determined before initiating treatment and on the third treatment day. Compounds that cause a decreased in blood glucose concentration during the study period at any of the doses that was greater by 20% or more than the decrease in blood glucose level, if any, occurring in control mice were considered active. KKA^y mice are rodent models of non-insulin dependent diabetes mellitus (Iwatsuka, H., Shino, A., and Suzuoki, Z.: General survey of diabetic features of yellow KK mice, *Endocrinol. Japon.* 17: 23-35, 1970).

Procedure 2: Compounds were administered orally to C57BL6J-*ob/ob* mice for 4 days. Compounds were mixed in the chow at 5 mg/g or unsupplemented chow was provided. The blood glucose concentration was determined before initiating treatment and on the fourth study day. Compounds that cause a decrease in blood glucose level during the study period that was greater by 20% or more than the decrease in blood glucose concentration, if any, occurring in control mice were considered active. *ob/ob* Mice are rodent models of non-insulin dependent diabetes mellitus (Coleman, D. L.: Diabetes-obesity syndromes in mice. *Diabetes* 31, Suppl. 1: 1-6, 1982).

Procedure 3: Compounds were tested for their ability to antagonize carrier mediated transport of 3-guanidinopropionic acid into rat brain synaptosomes. Rat brain synaptosomes were prepared as described (Fjalland, B., *Acta Pharmacol. et Toxicol.* 42: 73-76, 1978). Synaptosomes were incubated in Krebs Ringer bicarbonate buffer with 5 mM glucose and 0.1% bovine serum albumin, pH 7.4, for 5 min at 25°C with test compounds at a concentration of 1 mM and [4-¹⁴C]-3-guanidinopropionic acid. Compounds that decreased synaptosomal accumulation of [4-

SUBSTITUTE SHEET

^{14}C]-3-guanidinopropionic acid by $\geq 20\%$ were considered active. The ability of compounds to antagonize synaptosomal uptake of 3-guanidinopropionic acid was found to significantly correlate with the decrease in blood glucose concentration in KKA^y mice using Procedure 1. Thus antagonism in this assay was considered to be predictive of anti-NIDDM activity.

- 5 Effect of test compounds from Table 1 on blood glucose concentration in KKA^y mice was measured and is shown in Table 3. Data are shown as the ratio of post-treatment blood glucose levels in treated (T) and control (C) mice. T/C-values < 0.80 are considered active. Compounds were tested using Procedure 1. Stage 1 indicates the compound was tested at 1 mg/g; Stage 2, at 2 mg/g; Stage 5, at 5 mg/g.

SUBSTITUTE SHEET

TABLE 3

MOUSE INSULIN SENSITIZING SCREEN		
COMPOUND NUMBER (Table 1)	TEST STAGE	NFBG T/C
72	5X	0.56
6	5X	0.54
10	5X	0.52
11	5X	0.30
12	5X	0.30
13	5X	0.65
107	1 1	0.28 0.54
15	5X	0.37
73	5X 1	0.24 0.27
16	5X	0.76
18	5X	0.45
110	5X 1	0.56 0.79
75	5X	0.64
19	5X	0.50
20	5X	0.43
21	5X	0.64
24	5X	0.22
26	5X	0.70
27	5X	0.23
28	5X	0.33
29	3.3	0.20
82	5X	0.34
83	5X	0.28
86	5X	0.37

SUBSTITUTE SHEET

TABLE 3 (Cont'd)		
COMPOUND NUMBER (Table 1)	TEST STAGE	NFBG T/C
32	5X	0.35
33	5X	0.68
34	5X	0.40
36	5X	0.69
89	2X	0.58
90	5X	0.33
95	1	0.26
39	1	0.76
40	5X	0.37
41	5X	0.80
42	5X	0.64
43	5X 1	0.34 0.73
44	5X	0.38
45	5X	0.69
46	5X	0.45
47	5X	0.34
48	1	0.75
49	1	0.67
50	5X 1	0.12 0.42
51	5X	0.35
100	5X	0.71
52	5X	0.32
53	5X	0.36
54	5X	0.56
55	1 1 5X .3X	0.37 0.46 0.34 0.73

SUBSTITUTE SHEET

TABLE 3 (Cont'd)		
COMPOUND NUMBER (Table 1)	TEST STAGE	NFBG T/C
56	1	0.66
	1	0.66
	1	0.66
57	5X	0.77
101	5X	0.73
58	5X	0.53
59	5X	0.20
66	5X	0.47
67	5X	0.47
104	5X	0.62
70	5X	0.45
105	5X	0.37

SUBSTITUTE SHEET

The effect of Table 1 compounds on blood glucose concentration in *ob/ob* mice was measured and is shown in Table 4. Data are shown as the ratio of post-treatment blood glucose levels in treated (T) and control (C) mice. T/C-values <0.80 are considered active. Compounds were tested using Procedure 2.

5

TABLE 4

<u>Compound Id. # (Table 1)</u>		<u>Blood Glucose Response (T/C)</u>
10	71	0.40
	2	0.65
	3	0.74
	5	0.65
	14	0.46
15	25	0.68
	102	0.55
	97	0.72
	68	0.56
	103	0.72
20	60	0.75

The effect of Table 1 compounds on synaptosomal uptake of [4-¹⁴C]-3-guanidinopropionic acid is shown in Table 5. Compounds decreasing [4-¹⁴C]-3-guanidinopropionic acid uptake by >20% (i.e., <80% of control value) are considered active. Compounds were tested using Procedure 3.

TABLE 5

	UPTAKE INHIBITION			UPTAKE INHIBITION			UPTAKE INHIBITION	
	Compound # (Table 1)	% Control		Compound # (Table 1)	% Control		Compound # (Table 1)	% Control
5	71	74.00 76.00		76	72.20 72.20		94	4.00
	1	79.00		77	0.00 0.00		96	.70
	2	69.80		25	59.00 56.00		42	48.00
	3	78.00		30	47.40		43	74.90
10	4	76.00		78	13.00		46	35.30
	5	58.00		79	67.50		47	15.70
	6	52.00		80	54.40		49	72.80
	7	71.00		31	70.00		50	22.40
	8	69.10		81	64.70		51	53.30
15	9	3.00		82	6.50		52	30.00
	14	28.60		83	5.00 5.00		53	53.00
	107	72.00		84	73.00		57	22.00
	15	0.00		85	7.00		101	42.00
	73	42.00		86	53.00		58	7.80
20	74	3.00		115	2.00		97	50.00
	16	15.00		87	57.10		98	60.00
	17	79.00		36	64.00		60	29.00
	18	62.00		88	63.00		61	22.00
	110	64.00 64.00		37	55.00		62	45.00
25	75	42.50		117	52.00		63	59.00
	19	32.00		91	59.00		64	63.00
	20	63.00		92	10.50		103	68.00
	21	40.00		99	76.00		65	77.00
	22	68.00		38	50.00		66	60.00
30	23	42.00		93	7.00		119	48.00
	24	25.00						

SUBSTITUTE SHEET

The Table 2 compounds were tested for effects that are beneficial in the treatment or prevention of excess adiposity or obesity using one or more of three procedures.

Procedure 1: Compounds were administered orally to KKA^y mice for 3 days. Compounds were mixed in the chow at 1-5 mg/g or unsupplemented chow was provided. The body weight was determined before initiating treatment and on the third treatment day. Compounds that cause a decreased in body weight during the study period at any of the doses that was greater than the weight decrease, if any, occurring in control mice receiving unsupplemented chow were considered active. KKA^y mice are rodent models of obesity and diabetes (Iwatsuka, H., Shino, A., and Suzuoki, Z.: General survey of diabetic features of yellow KK mice, *Endocrinol. Japon.* 17: 23-35, 1970).

Procedure 2: Compounds were administered orally to C57BL6J-*ob/ob* mice for 4 days. Compounds were mixed in the chow at 5 mg/g or unsupplemented chow was provided. The body weight was determined before initiating treatment and on the fourth study day. Compounds that cause a decreased in body weight during the study period that was greater than the weight decrease, if any, occurring in control mice receiving unsupplemented chow were considered active. *ob/ob* Mice are rodent models of obesity and diabetes (Cawthorne, M. A.: The use of animal models in the detection and evaluation of compounds for the treatment of obesity, In: "Animal Models of Obesity", New York: Oxford University, pp. 79-90, 1979).

Procedure 3: Compounds were tested for their ability to antagonize carrier mediated transport of 3-guanidinopropionic acid into rat brain synaptosomes. Rat brain synaptosomes were prepared as described (Fjalland, B., *Acta Pharmacol. et Toxicol.* 42: 73-76, 1978). Synaptosomes were incubated in Krebs Ringer bicarbonate buffer with 5 mM glucose and 0.1% bovine serum albumin, pH 7.4, for 5 min at 25°C with test compounds at a concentration of 1 mM and [4-¹⁴C]-3-guanidinopropionic acid. Compounds that decreased synaptosomal accumulation of [4-¹⁴C]-3-guanidinopropionic acid by ≥20% were considered active. The ability of compounds to antagonize synaptosomal uptake of 3-guanidinopropionic acid was found to significantly correlate with weight loss in KKA^y mice using Procedure 1. Thus antagonism in this assay was considered to be predictive of anti-obesity activity.

The effect of the Table 2 compounds on body weight in KKA^y mice was tested and is shown in Table 6. Table 2 compounds were tested using Procedure 1. The first value indicates the compound was tested at 1 mg/g; the second value, at 2 mg/g; the fifth value, at 5 mg/g, etc. Percent (%) change is the body weight percent change.

SUBSTITUTE SHEET

-27-

TABLE 6

M.I.S.S. Obesity Data		M.I.S.S. Obesity Data		M.I.S.S. Obesity Data	
Table 2 Compound	% Change	Table 2 Compound	% Change	Table 2 Compound	% Change
81	-6.24	5	-6.87	7	-2.01
11	-3.91 -3.85	12	-10.77	13	-8.41
15	-2.05	120	-13.50 -3.77	16	-12.84
82	-12.74 -7.61	19	-3.03	123	-3.76 -4.14
84	-3.91	20	-11.53	21	-3.34
22	-1.94	25	-11.88	27	-1.90
28	-14.45	29	-11.74	30	-17.02
31	-1.74	91	-15.25	92	-19.29
95	-13.36	34	-6.38	35	-3.68
36	-4.17	37	-7.73	38	-2.40
115	-1.06	97	-0.85	99	-13.89
41	-4.97	104	-7.29	42	-1.59
43	-10.36 -2.44	44	-3.66	45	-1.10
46	-2.44	47	-4.91	48	-2.76
49	-7.36	50	-3.49	51	-1.28
52	-6.34	53	-13.30	54	-1.87
55	-1.53	56	-15.87 -5.86	57	-12.10
58	-11.66	59	-8.89	60	-4.26
61	-5.69 -4.66 -13.05 -0.21 -0.43	62	-0.94 -0.94 -0.94	63	-0.67
64	-9.16	65	-1.83	66	-0.81
67	-7.94	75	-1.74	76	-5.70
77	-2.79	117	-2.10	79	-2.31
118	-7.40				

SUBSTITUTE SHEET

The effect of the Table 2 compounds on body weight in *ob/ob* mice was tested and the values are shown in Table 7. Compounds were tested using Procedure 2.

TABLE 7

% Decrease in Body Weight

	<u>Compound (Table 2)</u>	<u>Control</u>	<u>Test Cmpd.</u>
5	80	1.6	10.1
	2	1.6	9.6
	3	2.7	8.7
	6	2.7	11.8
	14	2.7	13.2
10	86	1.7	13.0
	26	1.7	6.9
	29	1.7	8.1
	110	1.7	9.1
	106	0.5	6.7
15	68	0.5	7.5
	70	0.5	9.9
	74	0.5	1.1
	78	3.6	10.6
	73	3.6	4.0
20	111	3.6	5.9
	107	2.0	3.4
	108	2.0	4.0
	39	2.0	4.1
	69	2.0	11.8
25	71	2.0	3.3
	72	2.0	6.3
	17	4.0	5.1
	112	4.0	10.6
	113	4.0	8.5

The effect of the Table 2 compounds on synaptosomal uptake of [4-¹⁴C]-3-guanidinopropionic acid was tested and is shown in Table 8. Table 2 compounds decreasing [4-¹⁴C]-3-guanidinopropionic acid uptake by >20% (i.e., <80% of control value) are considered active. Table 2 compounds were tested using Procedure 3.

SUBSTITUTE SHEET

TABLE 8

Uptake Inhibition		Uptake Inhibition		Uptake Inhibition	
Table 2 Compound	% Control	Table 2 Compound	% Control	Table 2 Compound	% Control
80	74.00	86	0.00	47	48.00
1	79.00	26	59.00	48	74.90
2	69.80	32	47.40	52	35.30
3	78.00	87	13.00	53	15.70
4	76.00	88	67.50	55	72.80
6	58.00	89	54.40	56	22.40
5	52.00	33	70.00	57	53.30
8	71.00	90	64.70	58	30.00
9	69.10	91	6.50	59	53.00
10	3.00	92	5.00	63	22.00
14	28.60	93	73.00	116	42.00
120	72.00	94	7.00	64	7.80
16	0.00	95	53.00	65	42.00
82	42.00	128	2.00	66	23.00
83	3.00	96	57.10	106	50.00
114	15.00	129	1.40	68	60.00
18	79.00	115	64.00	69	29.00
19	62.00	98	63.00	70	22.00
123	64.00	39	55.00	71	45.00
84	42.50	112	52.00	72	59.00
20	32.00	100	59.00	73	63.00
21	63.00	101	10.50	111	68.00
22	40.00	109	76.00	74	77.00
23	68.00	40	50.00	75	60.00
24	42.00	102	7.00	113	48.00
25	25.00	103	4.00		
85	72.20	105	0.70		

SUBSTITUTE SHEET

CLAIMS

- 5 1. The use of a compound selected from Table 1 or a pharmaceutically acceptable salt thereof
for the preparation of a medicament useful in the treatment of non-insulin dependent (Type II)
diabetes mellitus.
2. The use of Claim 1 wherein a mode of administration is oral in an amount of 1-100 or 5-100
10 mg/kg/day.
3. The use of Claim 1 wherein the compound is administered as an admixture in the diet, a
pharmaceutical preparation, by injection or by implantable sustained released devices.
- 15 4. The use of a compound selected from Table 2 or a pharmaceutically acceptable salt thereof
for the preparation of a medicament useful in the treatment of excess adiposity or obesity.
5. The use of Claim 4 wherein a mode of administration is oral in an amount of 1-100 or 5-100
mg/kg/day.
20
6. The use of Claim 4 wherein the compound is administered as an admixture in the diet, a
pharmaceutical preparation, by injection or by implantable sustained released devices.
7. The use of a compound selected from Table 2 or a pharmaceutically acceptable salt thereof
25 for the preparation of a medicament useful in decreasing the fat content and for increasing the
muscle and protein content of animals, including humans.
8. The use of Claim 7 wherein a mode of administration is oral in an amount of 1-100 or 5-100
mg/kg/day.
30
9. The use of Claim 7 wherein the compound is administered as an admixture in the diet, a
pharmaceutical preparation, by injection or by implantable sustained released devices.

SUBSTITUTE SHEET



**CORRECTED
VERSION***

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁵ : A61K 31/11, 31/15, 31/155 A61K 31/165, 31/185, 31/19 A61K 31/195, 31/205	A3	(11) International Publication Number: WO 93/03714 (43) International Publication Date: 4 March 1993 (04.03.93)
(21) International Application Number: PCT/US92/06536 (22) International Filing Date: 11 August 1992 (11.08.92) (30) Priority data: 750,059 27 August 1991 (27.08.91) US 750,569 27 August 1991 (27.08.91) US (60) Parent Applications or Grants (63) Related by Continuation US 750,569 (CIP) Filed on 27 August 1991 (27.08.91) US 750,059 (CIP) Filed on 27 August 1991 (27.08.91) (71) Applicant (for all designated States except US): THE UPJOHN COMPANY [US/US]; 301 Henrietta Street, Kalamazoo, MI 49001 (US).		(72) Inventors; and (75) Inventors/Applicants (for US only): COLCA, Jerry, R. [US/US]; 8181 Contingo, Kalamazoo, MI 49009 (US). LARSEN, Scott, D. [US/US]; 2212 Sycamore Lane, Kalamazoo, MI 49008 (US). MEGLASSON, Martin, Durham [US/US]; 5337 Whippoorwill, Kalamazoo, MI 49002 (US). TANIS, Steven, P. [US/US]; 7601 Farmington Avenue, Kalamazoo, MI 49002 (US). (74) Agent: CORNELGIO, Donald, L.; Corporate Intellectual Property Law, The Upjohn Company, 301 Henrietta Street, Kalamazoo, MI 49001 (US). (81) Designated States: AU, BB, BG, BR, CA, CS, FI, HU, JP, KP, KR, LK, MG, MN, MW, NO, PL, RO, RU, SD, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, SN, TD, TG). Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i> (88) Date of publication of the international search report: 10 June 1993 (10.06.93)
(54) Title: A METHOD FOR TREATMENT OF METABOLIC DISORDERS		
(57) Abstract <p>A method for treating or preventing non-insulin (Type II) diabetes mellitus by administering to an animal, including humans, a compound selected from Table 1 or a pharmaceutically acceptable salt thereof; and a method for treating or preventing excess adiposity or obesity by administering to an animal, including humans, a compound selected from Table 2 or a pharmaceutically acceptable salt thereof.</p>		

* (Referred to in PCT Gazette No. 14/1993, Section II)

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	FR	France	MR	Mauritania
AU	Australia	GA	Gabon	MW	Malawi
BB	Barbados	GB	United Kingdom	NL	Netherlands
BE	Belgium	GN	Guinea	NO	Norway
BF	Burkina Faso	GR	Greece	NZ	New Zealand
BG	Bulgaria	HU	Hungary	PL	Poland
BJ	Benin	IE	Ireland	PT	Portugal
BR	Brazil	IT	Italy	RO	Romania
CA	Canada	JP	Japan	RU	Russian Federation
CF	Central African Republic	KP	Democratic People's Republic of Korea	SD	Sudan
CG	Congo	KR	Republic of Korea	SE	Sweden
CH	Switzerland	KZ	Kazakhstan	SK	Slovak Republic
CI	Côte d'Ivoire	LI	Liechtenstein	SN	Senegal
CM	Cameroon	LK	Sri Lanka	SU	Soviet Union
CS	Czechoslovakia	LU	Luxembourg	TD	Chad
CZ	Czech Republic	MC	Monaco	TG	Togo
DE	Germany	MG	Madagascar	UA	Ukraine
DK	Denmark	ML	Mali	US	United States of America
ES	Spain	MN	Mongolia	VN	Viet Nam
FI	Finland				

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 92/06536

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) ⁶		
According to International Patent Classification (IPC) or to both National Classification and IPC		
Int.Cl. 5	A61K31/11; A61K31/185;	A61K31/15; A61K31/19; A61K31/155; A61K31/195; A61K31/165; A61K31/205
II. FIELDS SEARCHED		
Minimum Documentation Searched ⁷		
Classification System	Classification Symbols	
Int.Cl. 5	A61K	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁸		
III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹		
Category ¹⁰	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
X	CHEM. PHARM. BULL. vol. 18, no. 8, 1970, pages 1636 - 1642 FUJIHIRA, E., ET AL 'EFFECT OF LONG-TERM FEEDING OF TAURINE IN HEREDITARY HYPERGLYCEMIC OBESE MICE' see the whole document see the whole document -----	1-6
<p>¹⁰ Special categories of cited documents:</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"A" document member of the same patent family</p>		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search 25 NOVEMBER 1992		Date of Mailing of this International Search Report 12. 11. 92
International Searching Authority EUROPEAN PATENT OFFICE		Signature of Authorized Officer KLAVER T.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 92/06536

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

For further information please see form PCT/ISA/206 dated 03.02.93.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-9 partially

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.